REMARKS

Claims 1-21 are pending in the present application. The abstract has been amended to correct a typographical error. No new matter has been added by this amendment.

DRAWINGS

The Examiner has stated that the drawings are objected to by the draftsperson. Applicants will submit formal drawings upon the determination of allowable subject matter.

THE 35 U.S.C. §112, FIRST PARAGRAPH REJECTION

The Examiner has rejected claims 1-21 under 35 U.S.C. §112, first paragraph, as lacking enablement, stating that the specification "does not reasonably provide enablement for the use of the said retroviral vector and/or the cell for therapeutic purposes in *in vivo* controlled delivery of diagnostic and therapeutic agents." (See Office Action page 3). The Examiner further states that "the invention of the claims 1-21 is intended to be used for the purpose of gene therapy in mammals and/or humans." (See Office Action page 4).

Applicants traverse. Claim 1 recites "[a] nucleic acid molecule comprising a sequence encoding a recombinase and a signal sequence recognized by said recombinase." Neither claim 1 nor any other pending claim recites the limitation that the claimed nucleic acid molecules are intended for the use of gene therapy in mammals. The Examiner states that "[t]he claims encompass gene therapy, because one of the purposes of the retroviral vector comprising heterologous nucleic acid, as disclosed by the specification, is for therapeutic purposes..." and that "[t]he specification does not disclose any other purpose or utility for transducing the mammalian and/or human cells and for expressing heterologous nucleic acids encoded on the retroviral vectors of the instant invention. (Emphasis added; See Office Action page 4). While the specification does disclose embodiments of the present invention that are useful in therapeutic applications (see, *e.g.,* Specification at pg. 3, lines 1-3; and page 21, line 29 to page 24, line 11), and Applicants reserve the right to pursue such embodiments in additional applications, the pending claims are not drawn to such embodiments. Applicants also assert that other purposes or utilities of the retroviral vectors recited in claims 1-21 are disclosed in and fully enabled by the specification. The specification recites that the vectors of the present invention are useful as research reagents; in the controlled delivery of diagnostic agents; in

detection assays (*e.g.*, chromosomal mapping, cell and tissue typing, forensic biology); in predictive medicine (*e.g.*, diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenomics); in production of therapeutic molecules either from cells or whole animals; in production of agricultural products; and in prevention of spread or theft of transgenic animals or plants. (See, *e.g.*, page 3, lines 1-3 and page 20, lines 11-22).

Applicants respectfully submit that any person skilled in the art would be able to make and use the invention commensurate in scope with claims 1-21. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

THE 35 U.S.C. §103 REJECTION

The Examiner has rejected claims 1-21 under 35 U.S.C. §103(a), as being obvious over Sauer and Gagneten *et al.* (hereinafter "Gagneten") in view of Miyoshi *et al.* (hereinafter "Miyoshi").

Applicants traverse. The Examiner admits that "Sauer does not teach the self excising Cre of the instant invention," that "Gagneten *et al.* do not teach the transient expression of Cre by self excision," and that "Miyoshi *et al.* do not teach their SIN vectors in the context of the Cre/lox system." (See Office Action at pages 11-12). The Examiner further states that:

> ... it would have been obvious to one or ordinary skill in the art to be motivated to use the Cre/lox system to delete the Cre recombinase gene itself, with a reasonable expectation of success, to inactivate further recombination that might lead to genomic instability and toxicity, once the vector transfected the cell and expressed the Cre recombinase, following the example of the SIN lentiviral vectors, in which case it was successfully demonstrated that SIN lentiviral vectors improve safety of using retroviral vectors.

(See Office Action page 12).

Applicants respectfully submit that the Examiner has mischaracterized the SIN vectors of Miyoshi. Miyoshi generated a *tat*-independent, self-inactivating (SIN) lentiviral vector by replacing the U3 region of the 5' long terminal repeat (LTR) with a cytomegalovirus (CMV) promoter and by deleting 133 bp in the U3 region of the 3'UTR. (See, *e.g.*, p. 8150). This manipulation was performed to minimize the possibility that the transduced virus would generate provirus, which would in turn randomly integrate into the host genome. (See, *e.g.*, p. 8150). While Miyoshi disclose that, in the SIN vector, the transcriptional unit from the LTRs in a

provirus is eliminated (see, *e.g.*, p. 8151), this reference does not teach or suggest that the SIN vector is capable of acting upon itself to prevent transcription of the gene(s) contained within the vector, such as GFP. Thus, while the SIN vectors may be safer because the incidence of proviral replication is theoretically reduced, the SIN vectors of Miyoshi do nothing to prevent cell toxicity caused by sustained expression of a recombinase gene such as Cre. Simply put, if one of skill in the art were to insert a recombinase gene into the SIN vectors of Miyoshi, cell toxicity would not be prevented since the expression of the recombinase would be sustained even in the presence of recombinase activity.

In marked contrast, the present invention relates in part to a nucleic acid molecule, or a cell comprising said nucleic acid molecule, encoding a recombinase and a signal sequence (such as lox) recognized by the recombinase. In the present invention, an expressed recombinase can trigger deletion of both a target bearing flanking lox sites and its own coding sequence without toxicity (see *e.g.*, Figs 7A-D).

Indeed, Miyoshi teaches away from the present invention by disclosing SIN vectors that induce long-term protein expression, rather than expression of Cre for a limited duration in order to prevent genomic instability and toxicity. For example, Miyoshi shows sustained expression of green fluorescent protein (GFP) in adult rat brain six weeks after injection of SIN vectors. (*See, e.g.*, Figure 4). Miyoshi also show GFP expression in rat retina twelve weeks after injection of SIN vectors. (*See, e.g.*, Figure 5).

Therefore, Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art how to use the long-term expression vectors of Miyoshi in the context of the Cre/lox system as taught by Sauer and Gagneten in order to avoid genomic instability and toxicity by prevention of sustained recombinase activity. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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